SUMMARY OF SAFETY AND EFFECTIVENESS DATA
FOR A SUPPLEMENTAL PREMARKET APPROVAL APPLICATION

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Excimer Laser System
Device Trade Name:	LADARVision®4000 Excimer Laser System
Applicant's Name and Address:	Alcon, Inc. 2501 Discovery Drive, Suite 500 Orlando, FL 32826
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P970043/S15
Date of Notice of Approval to Applicant:	June 29, 2004

The LADARVision®4000 Excimer Laser System was approved on November 2, 1998 for the indication of photorefractive keratectomy (PRK) for the reduction or elimination of mild to moderate myopia of between -1.00 and -10.00D sphere and less than or equal to -4.00D astigmatism at the spectacle plane, the combination of which must result in an attempted correction of between -0.50 and -10.00D spherical equivalent (SE) at the spectacle plane where the sphere or cylinder is at least 1.00D (P970043). On May 9, 2000, the device was approved for the indication of laser in-situ keratomileusis (LASIK) for the reduction or elimination of myopia of less than -9.00D sphere and -0.50 to less than -3.00D astigmatism at the spectacle plane (P970043/S5). On September 22, 2000, the device was approved for the indication of LASIK for the reduction or elimination of refractive error of less than or equal to +6.00D sphere and -6.00D astigmatism at the spectacle plane (hyperopia with or without astigmatism and mixed astigmatism) (P970043/S7).

On October 18, 2002, the LADARVision®4000 system was also approved for wavefront-guided LASIK for the reduction or elimination of myopia up to -7.00D sphere with less than -0.50D astigmatism at the spectacle plane (P970043/S10). The sponsor submitted this supplement to further expand the clinical indications to include wavefront-guided CustomCornea® LASIK for myopia with astigmatism. The updated clinical data to support the expanded indication is provided in this summary. The pre-clinical test results were provided in the original PMA and prior PMA supplements. Written requests for copies of the SSED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20857 under Docket # 02M-0487 or you may download these files from the internet site http://www.fda.gov/cdrh/pdf/p970043.pdf.

II. INDICATIONS FOR USE

The LADARVision®4000 Excimer Laser System is indicated for wavefront-guided Laser Assisted In-Situ Keratomileusis (LASIK):

- for the reduction or elimination of myopic astigmatism up to -8.00D sphere with -0.50D to -4.00D cylinder and up to -8.00D spherical equivalent at the spectacle plane;
- in patients who are 21 years of age or older; and
- in patients with documented stability of refraction for the prior 12 months, as demonstrated by a change in sphere and cylinder of less than or equal to 0.50D for a spherical equivalent up to –6.00D and less than or equal to 0.75D for a spherical equivalent greater than –6.00D.

III. CONTRAINDICATIONS

Wavefront-guided LASIK is contraindicated in:

- pregnant or nursing women.
- patients with autoimmune, collagen vascular, or immunodeficiency disease.
- patients with signs of keratoconus.
- patients who are taking one or both of the following medications: isotretinoin (Accutane[1]) or amiodarone hydrochloride (Cordarone[2]).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

A. Wavefront Measurement Device (WMD)

The first step in performing CustomCornea® LASIK surgery is to perform a wavefront examination on the patient using a wavefront measurement device (WMD) compatible with the LADARVision®4000 Excimer Laser System. At the present time, the only compatible WMD is the Alcon® LADARWave® CustomCornea® Wavefront System, the wavefront measurement device used in the clinical trial.

The LADARWave® CustomCornea® Wavefront System is indicated for measuring, recording, and analyzing visual aberrations (such as myopia, hyperopia, astigmatism, coma and spherical aberration) and for displaying refractive error maps of the eye to assist in prescribing refractive corrections. This device is enabled to export wavefront data and associated anatomical registration information to a compatible treatment laser with an indication for wavefront-guided refractive surgery.

[1] Accutane Reg. TM of Hoffman-La Roche Inc
[2] Cordarone Reg. TM of Sanofi-Synthelabo Inc.

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Essential features of the compatible WMD are as follows:

1. *Patient Fixation and Fogging*

   The WMD includes a fixation optical subsystem that provides the patient with an unambiguous fixation point. In addition, the fixation subsystem includes adjustable optics to compensate for the patient's inherent refractive error. The optics are used to "fog" the eye, first clarifying the fixation target and then it optically adjusts beyond the patient's far point to minimize accommodation.

2 *Centration*

   Prior to dilation, the WMD is used to record the geometric relation between the natural daytime pupil center and the limbus of the eye. This information is then used to center the wavefront measurement and subsequent ablative treatment on the natural line of sight.

3. *Wavefront Measurement*

   The WMD measures the wavefront profile of the eye with a high degree of accuracy and characterizes the profile using Zernike polynomials. The pupil must be large enough so that valid wavefront data can be obtained over a large area. Higher-order aberrations are more significant at night when the pupil is naturally larger. Therefore, when treating these aberrations, measurement over a large pupil provides the greatest utility.

4. *Registration*

   The WMD uses synchronized video imagery and on-screen software reticules to record the relationship of the wavefront data to the limbus of the eye and to ink marks applied to the sclera just before the wavefront exam. This registration information is used to position the excimer ablation profile at the right corneal location and cyclotorsional angle.

5. *Data Export*

   The WMD has the ability to export the wavefront examination data as an electronic file to floppy disk for transfer to the LADARVision®4000 system. The electronic file is structured in a specific format and contains essential patient information, centration/registration information, and the detailed aberration data. In addition, the electronic file is encrypted in a manner that can only be deciphered by the LADARVision®4000 system.

B. Microkeratome

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing via a premarket notification. The device used in this study consists of a head, plates, ring, handle, wrenches, shaft, motor, hand-piece, disposable blades, and power supply with footswitches and power cords. The system is completed with the applanation lens set, tonometer, corneal storage jar, optical zone marker, spatula, stop attachment, and digital thickness gauge.

The microkeratomes used in the clinical trial included the Amadeus[3] (manufactured by Surgical Instruments Systems, Ltd. and owned by Advanced Medical Optics), BD K-4000[4] (manufactured by Becton-Dickinson), Hansatome[5] (manufactured by Bausch & Lomb), and the Moria[6] M2 (manufactured by Moria).

C. CustomCornea® Surgery Planning Software

The CustomCornea® Surgery Planning Software is a stand-alone computer application linking the diagnostic wavefront data with the surgical treatment on the LADARVision®4000 Excimer Laser System. The planning software allows refinement of surgical parameters within the approved wavefront-guided indication for the LADARVision®4000 system and calculation of ablation depth.

After completing the surgery planning tasks, the planned treatment file is transferred to the LADARVision®4000 system. The LADARVision®4000 system software imports the treatment file, enforces the eligibility, calculates the excimer treatment pattern, and performs the surgery.

Software version 1.0, used in the clinical trial, is the commercial release version.

D. LADARVision®4000 Excimer Laser System

The LADARVision®4000 excimer laser beam is of Gaussian profile and small in diameter (<0.90mm). Corneal sculpting is achieved by delivering hundreds to thousands of excimer laser pulses to the eye in a complex pattern of spatially overlapping spots, and precision of this process depends on accurate placement of the laser pulses. The LADARVision®4000 Excimer Laser System incorporates the LADARTracker® closed-loop laser radar eye-tracking system to track and compensate for patient eye motion, including saccadic movements, during procedures so that each excimer laser pulse is delivered to the appropriate location on the cornea.

Rather than the refractive correction being manually entered by the physician based on phoropter refraction, the CustomCornea® treatment requires that the pre-operative aberrations in the eye be measured with a wavefront measurement device. The treatment is based on Zernike data derived from a wavefront measurement device, including treatment of lower-order sphere and astigmatism components and higher-order components, such as coma and spherical aberration. The electronic file that the LADARVision®4000 system receives from the wavefront measurement device includes the following information:

- Patient information, including name, identification number, and clinical prescription.
- Eye information, including OD/OS and the geometric relationship of the wavefront data to the limbus and to the pupil center.
- Wavefront information, including a Zernike polynomial representation of the wavefront and the physical radius of that description.

[3] *Amadeus* Reg. TM of SIS AG, Surgical Instrument Systems
[4] *BD K-4000* TM of Becton, Dickinson and Company
[5] *Hansatome* Reg. TM of Hansa Research & Development, Inc.
[6] *Moria* Reg. TM of Moria SA

The excimer laser beam characteristics (i.e., pulse energy, firing rate, fluence distribution at the treatment plane) are the same for Conventional and CustomCornea® treatment modalities. The Conventional LADARVision®4000 system treatment utilizes sphere, cylinder and axis components entered manually by the operator to generate the ablation profile. The CustomCornea® LASIK shaping algorithm utilizes aberration information unique to a given eye that is obtained from the WMD to guide the ablation of the cornea. The wavefront information is registered to the anatomical geometry of the eye using the WMD while the patient is sitting upright. This registered alignment information is passed to the LADARVision®4000 system, which both permits for the compensation of this alignment information due to the natural cyclotorsion incurred when the patient assumes a prone position and uses the geometry information to accurately position the customized ablation profile on the eye.

The approved CustomCornea® ablation zone parameters, as used in the clinical trial, include a 6.5mm optical zone with a 1.25mm blend zone for a 9mm total ablation zone.

CustomCornea® myopic astigmatism corrections are locked out above -9.75D sphere, above -5.00D cylinder, and above -10.63D spherical equivalent. There are insufficient safety and effectiveness data above -8.00D sphere, above -4.00D cylinder, and above -8.00D spherical equivalent. A flag warning will appear when a correction above the approved indication is selected.

Features and components of the LADARVision®4000 Excimer Laser System include:

1. *Excimer Laser*

   This argon fluoride excimer laser produces 10 nanosecond pulses of ultraviolet radiation at a wavelength of 193 nanometers. The laser repetition rate is between 50 and 60 pulses per second. The characteristics of the laser beam at the corneal treatment plane include: a pulse energy of 2.4 to 3.0mJ; a beam diameter of less than 0.90mm; and average fluence of 180 to 240 mJ/cm^2.

2. *Optical transmission system*

   The excimer laser passes through an optical telescope, followed by reflection off a series of mirrors, which position the excimer laser pulses in the correct locations at the treatment plane.

3. *Energy monitoring/control*

   The laser pulse energy is monitored to ensure delivery of 2.4 to 3.0 mJ to the eye prior to surgery and during ablation.

4. *Gas handling*

   The excimer laser enclosure holds the laser, gas bottle, and gas-plumbing manifold. The gas bottle contains the pre-mixed gas, including argon, fluorine, and neon as the buffer gas. Gas flow is regulated through the system, responding to commands from the laser control electronics board.

5. *Active Closed-Loop Laser Radar Eye Tracking System*

The LADARTracker® system actively tracks the position of the eye by irradiating it with pulses of 905 nm infrared "eye-safe" energy and analyzing characteristics of the returning laser radiation. This measurement occurs 4000 times each second to detect even rapid eye motion before significant movement of the cornea has occurred. The LADARTracker® system actively compensates for the detected motion, rather than simply disabling the laser when the eye position exceeds some tolerated error range.

6. *Operating microscope*

The stereo viewing operating microscope is located in the optics head. The dual optical paths are independent of the excimer beam path and the tracker mirrors.

7. *Fixation target*

A visible fixation target is mounted in the system to facilitate the patient looking in the direction of the excimer beam. The fixation target consists of a red light emitting diode (LED), a pinhole aperture, an edge-illuminated reticule, and a lens.

8. *Motorized Bed and Cross Beam Patient Positioning*

A motorized patient bed, which moves on X, Y and Z axes, smoothly and rapidly positions the patient and facilitates bilateral procedures. Cross beam Class I lasers are used to place the cornea at a predetermined height for proper ablation.

9. *System Software Control*

The LADARVision®4000 system software enables the user to: properly center the treatment; make adjustments in the X and Y axes; adjust for cyclotorsion and correctly reference astigmatism; place a hinge guard to protect the flap during surgery; and properly match the alignment of the wavefront map to the ablation.

Software versions 5.09 and 5.11 were used in the clinical trial. The commercial release version is 5.13 (Build 7).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several other alternatives for the correction of myopia and astigmatism:

Automated lamellar keratoplasty (ALK)
Contact Lenses
Conventional Laser in-situ keratomileusis (LASIK - based on phoropter refraction)
Conventional Photorefractive Keratectomy (PRK - based on phoropter refraction)
Radial Keratotomy (RK)
Spectacles

Each alternative has its own advantages and disadvantages. A prospective patient should fully discuss with his/her care provider these alternatives in order to select the correction method that best meets his/her expectation and lifestyle.

VII. MARKETING HISTORY

The device has been marketed for the current indication of myopic astigmatism in the following countries: Australia, Belgium, Czech Republic, France, Germany, Greece, Italy, Korea, Mexico, Netherlands, Norway, Spain, Sweden, United Kingdom. In general, the device has been marketed in the following countries: Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Cyprus, Czech Republic, France, Germany, Greece, Hong Kong, India, Italy, Korea, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, Puerto Rico, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom, United States, and Vietnam. The LADARVision®4000 system has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects associated with LASIK include: loss of best-spectacle corrected visual acuity (BSCVA); worsening of patient complaints such as double vision, sensitivity to bright lights, increased difficulty with night vision, fluctuations in vision; increase in intraocular pressure; corneal haze; secondary surgical intervention; corneal infiltrate or ulcer; corneal epithelial defect; corneal edema; problems associated with the flap including a lost, misplaced or misaligned flap; retinal detachment; and retinal vascular accidents.

Please refer to the complete listing of adverse events and complications observed during the clinical study, which are presented on page 23 of the clinical study section.

IX. SUMMARY OF PRECLINICAL STUDIES

A series of pre-clinical tests were conducted on the LADARVision®4000 system upon initial development for conventional refractive surgery procedures prior to entry into human clinical trials. Those tests included algorithm simulations and ablation profiles using plastic blocks, as well as animal testing. Please refer to the SSED for the original PMA (P970043) for a summary of the pre-clinical testing.

A series of pre-clinical tests were conducted on the CustomCornea® algorithms prior to entering human clinical trials. These tests included algorithm validation, which tested the ablation shot pattern in both an ablation simulation program and actual PMMA substrate (surrogate) ablation experiments. Excellent agreement was demonstrated between the results obtained from PMMA substrate and simulated ablations. The CustomCornea® algorithm reproduced the results obtained with the existing conventional algorithm and demonstrated accuracy in performing more complex ablations. This algorithm validation provided sufficient evidence to proceed to human clinical trials.

X. SUMMARY OF CLINICAL STUDIES

The Sponsor performed a clinical study of wavefront-guided CustomCornea® LASIK correction of myopia and astigmatism using the LADARVision®4000 Excimer Laser System in the U.S. under an investigational device exemption application (IDE G950213). In addition, one foreign site collected data under an investigational device application in Canada using a protocol that was the same as the U.S. protocol in terms of the inclusion and exclusion criteria, study procedures, patient measurements, and the treatment applied to the

eye. Therefore, data from the U.S. and Canadian centers were pooled for the analysis of safety and effectiveness. A summary of the clinical trial is presented below.

A. Study Objective

The primary objective of the clinical investigation of the LADARVision®4000 Excimer Laser System for wavefront-guided CustomCornea® LASIK correction of myopia and astigmatism was to establish safety and effectiveness. Secondary study objectives included 1) to obtain preoperative and postoperative wavefront data to aid in the understanding of refractive and corneal shape changes as a result of the surgery and postoperative healing; and 2) to analyze the relationship between quality of vision indicators calculated from the wavefront data and clinical outcomes.

B. Study Design

This study was a prospective, non-randomized, unmasked, and multi-center trial where the primary control was the preoperative state of the treated eye for comparison with postoperative parameters in the same eye.

C. Inclusion and Exclusion Criteria

Recruited subjects had the study details and follow-up requirements explained to them and were asked to sign an Informed Consent Document preoperatively. To be eligible for inclusion into the study, the spectacle plane refraction must have had a sphere between +6.00 and -15.00D and a cylinder between 0 and -6.00D with a manifest refraction spherical equivalent (MRSE) between +6.00 and –15.00D. Enrollment of myopic astigmatic eyes in the study occurred over the range of up to -9.75D sphere and -0.50D to -5.00D cylinder with an MRSE up to -10.63D.

Stability of refraction must have been established and documented using previous clinical records or measurement of spectacles. Stability was demonstrated by a change in sphere and cylinder over the prior 12 months of less than or equal to 0.50D for eyes with a MRSE up to 6.00D of myopia, or less than or equal to 0.75D for eyes with a MRSE greater than 6.00D of myopia. In addition, the manifest and cycloplegic refraction measured at the preoperative examination must have been within 0.50D of each other in the sphere and cylinder components for eyes with a MRSE less than 7.00D of myopia, or within 0.75D for eyes with a MRSE greater than or equal to 7.00D of myopia.

The manifest refraction could not differ by more than 1.00D in sphere or cylinder from the attempted correction determined by the Wavefront Measurement Device (WMD). Subjects whose eyes could not be assessed by the WMD, including an inability to obtain a clear and complete image, were excluded from the study.

Subjects must have been at least 18 years of age. Both eyes must have had a best-spectacle corrected visual acuity (BSCVA) of 20/25 or better. Subjects must have been willing to return for scheduled follow-up examinations for 6 months after surgery and have their eyes pharmacologically dilated at each visit. Subjects who were contact lens wearers were requested to discontinue contact lens wear in both eyes at least 2 to 3 weeks depending upon the lens type prior to the preoperative examination. Subjects who

had worn RGP and PMMA lenses were required to have two examinations conducted 2-3 weeks apart to show stability of refraction without lens wear.

All eyes were required to be treated for emmetropia. All surgeries performed in the study were subject to approval by the Sponsor. The calculated residual posterior stromal corneal thickness must have been at least 250 microns in all treated eyes.

Patients with the following conditions could not be included in the study: previous intraocular, corneal or strabismus surgery; glaucoma or glaucoma filtering surgery; history of or active clinically or visually significant ocular disease or pathology; clinically significant corneal scar within the ablation zone or other corneal abnormality such as recurrent erosion or severe basement membrane disease; progressive or unstable myopia or keratoconus; irregular corneal astigmatism; history of herpes keratitis; autoimmune disease, connective tissue disease, clinically significant atopic syndrome or diabetes; use of chronic systemic corticosteroids or other immunosuppressive therapy; use of ophthalmic medications other than artificial tears for treatment of an ocular pathology; use of systemic medication with significant ocular side effects; severe dry eye syndrome unresolved by treatment; known allergy to study medications; pregnant or lactating females; unable to achieve a pupillary dilation of at least 7mm; at risk for angle closure; or, participation in another ophthalmic clinical trial.

D. Study Plan, Patient Assessments, and Efficacy Criteria

All patients were expected to return for follow-up at 1 day, 1 week, and 1, 3 and 6 months postoperatively. All CustomCornea® treatments in the study were conducted with use of an optical zone of 6.5mm with a blend zone of 1.25mm for a total ablation zone of 9mm.

Patients were permitted to have their fellow eyes treated on the same day as the primary eye or any time thereafter provided there was no active complication or adverse event for the primary eye.

Retreatments were permitted after the 3-month follow-up visit. Retreatment criteria included:

(1) An uncorrected visual acuity (UCVA) worse than 20/25 or residual sphere or cylinder greater than or equal to 0.50D at both of the two most recent consecutive visits that are at least one month apart.

(2) Stable refraction with the sphere and cylinder components within 0.50D on two most recent consecutive visits that are at least one month apart.

(3) Stable UCVA, i.e., within one line on two consecutive visits at least one month apart.

(4) The eligibility criteria are met and an ophthalmic evaluation (including visual acuity, manifest refraction, and slit lamp) is done to establish the preoperative condition of the eye.

(5) Prior written approval from the sponsor of the study.

(6) Subject's signature on a separate Retreatment Informed Consent document, wherein the subject is informed of the risks associated with retreatment.

Retreatment for the purpose of correcting residual refractive error was not considered a treatment failure. Results of retreated eyes were analyzed separately from the primary treatment population.

No other ocular surgery procedures were allowed unless deemed medically necessary by the investigator. The investigator was required to notify the sponsor prior to any secondary surgical intervention, except in the case of an emergency in which case notification must occur as soon as possible.

In the event of a miscreated flap with the microkeratome, which is an adverse event in the study, a second cut with the microkeratome could be performed and the laser ablation procedure may be completed after a minimum of 3 months. Approval from the Medical Monitor was required prior to treating an eye with a miscreated flap.

Preoperatively, the patient's medical and ocular histories were recorded. The objective parameters measured during the study included: uncorrected visual acuity, best spectacle corrected visual acuity, pupil size, vertex distance, manifest and cycloplegic refraction, wavefront measurement, contrast sensitivity, intraocular pressure, angle assessment, slit lamp and dilated fundus examination. The following objective parameters were collected preoperatively and only as needed postoperatively: corneal thickness, corneal topography, and keratometry. The subjective parameters measured during the study included a subjective questionnaire.

The primary efficacy variables for this study were improvement of uncorrected visual acuity, predictability and stability of manifest refraction spherical equivalent, reduction of wavefront error, and subject satisfaction.

E. Study Period, Investigational Sites, and Demographics

1. Study Period and Investigational Sites

Subjects in this study were treated between October 15, 2002 and May 29, 2003. The primary cohort consisted of 331 eyes including 74 spherical myopic eyes with less than -0.50D cylinder and 257 myopic astigmatic eyes with -0.50D to -5.00D cylinder based on manifest refraction. The effectiveness cohort consisted of 232 myopic astigmatic eyes with -0.50D to -5.00D cylinder, and the safety cohort consisted of all 331 eyes.

All eyes were treated based on the Zernike data from the wavefront measurement system including lower-order aberrations, such as sphere and cylinder and higher-order aberrations, such as spherical aberration and coma. There were six investigational sites including five U.S. sites and one Canadian site.

2. Demographics

The demographics of the CustomCornea® study (Table 1) are typical for a refractive surgery trial performed in the U.S. The mean subject age was 37 years with a range from 19 to 57 years. The gender distribution was 59.2% males and 40.8% females. The racial distribution consisted of 94.6% Caucasian, 2.4% Asian, 1.8% Hispanic, 0.6% Black, and 0.6% East Indian. The treatment of right and left eyes was approximately equal. The majority (65.3%) of subjects had a history of soft contact lens wear, 24.2% had no history of contact lens wear, and 10.6% had a history of RGP or PMMA lens wear. Preoperative patient characteristics that were found to be associated with outcomes are discussed in Section X.F.2.j.

Table 1. Demographics

331 Eyes of 167 Enrolled Subjects		
Age (In Years) Average ± Standard Deviation Minimum to Maximum	37.0 ± 9.0 19 to 57	
Race	**N**	**% Eyes**
Asian	8	2.4%
Black	2	0.6%
Caucasian	313	94.6%
East Indian	2	0.6%
Hispanic	6	1.8%
Gender: Female	135	40.8%
Male	196	59.2%
Eye: Left	166	50.2%
Right	165	49.8%
Contact Lens History: None	80	24.2%
PMMA	4	1.2%
RGP	31	9.4%
Soft	216	65.3%

PMMA = Polymethyl methacrylate; RGP = Rigid gas permeable

F. Data Analysis and Results

1. Preoperative Characteristics

Table 2 contains the number of eyes stratified by preoperative manifest sphere and cylinder.

Table 2. Preoperative Manifest Refraction Stratified By Sphere & Cylinder for All Eyes

		CYLINDER (D)						
SPHERE (D)		0 to -0.49	-0.50 to -0.99	-1.0 to -1.99	-2.0 to -2.99	-3.0 to -3.99	-4.0 to -5.0	TOTAL
0.0 to -0.99	n/N	0/331	3/331	11/331	8/331	2/331	1/331	25/331
	%	0.0%	0.9%	3.3%	2.4%	0.6%	0.3%	7.6%
-1.0 to -1.99	n/N	16/331	14/331	20/331	7/331	3/331	2/331	62/331
	%	4.8%	4.2%	6.0%	2.1%	0.9%	0.6%	18.7%
-2.0 to -2.99	n/N	8/331	16/331	20/331	8/331	4/331	0/331	56/331
	%	2.4%	4.8%	6.0%	2.4%	1.2%	0.0%	16.9%
-3.0 to -3.99	n/N	18/331	16/331	21/331	1/331	1/331	1/331	58/331
	%	5.4%	4.8%	6.3%	0.3%	0.3%	0.3%	17.5%
-4.0 to -4.99	n/N	7/331	18/331	19/331	2/331	0/331	0/331	46/331
	%	2.1%	5.4%	5.7%	0.6%	0.0%	0.0%	13.9%
-5.0 to –5.99	n/N	11/331	8/331	12/331	2/331	1/331	0/331	34/331
	%	3.3%	2.4%	3.6%	0.6%	0.3%	0.0%	10.3%
-6.0 to –6.99	n/N	6/331	5/331	9/331	0/331	0/331	0/331	20/331
	%	1.8%	1.5%	2.7%	0.0%	0.0%	0.0%	6.0%
-7.0 to –7.99	n/N	4/331	12/331	2/331	1/331	0/331	0/331	19/331
	%	1.2%	3.6%	0.6%	0.3%	0.0%	0.0%	5.7%
-8.0 to –8.99	n/N	3/331	2/331	2/331	0/331	0/331	0/331	7/331
	%	0.9%	0.6%	0.6%	0.0%	0.0%	0.0%	2.1%
-9.0 to –9.75	n/N	1/331	0/331	3/331	0/331	0/331	0/331	4/331
	%	0.3%	0.0%	0.9%	0.0%	0.0%	0.0%	1.2%
TOTAL	n/N	74/331	94/331	119/331	29/331	11/331	4/331	331/331
	%	22.4%	28.4%	36.0%	8.8%	3.3%	1.2%	100.0%

(D) = Diopter

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2. Postoperative Results

a. Accountability

Table 3 shows the accountability for this study, which was 100% at all postoperative intervals. All 331 eyes from the safety cohort and all 232 myopic astigmatic eyes from the effectiveness cohort were available for analysis through the 6-month postoperative visit.

Table 3. Accountability at Each Visit

		1 MONTH	3 MONTHS	6 MONTHS
Total Enrolled: Primary	n	167	167	167
Fellow	n	164	164	164
Total	N	331	331	331
Available for Analysis	n	331	331	331
	%	100.0%	100.0%	100.0%
Not Eligible for Interval / In Process:	n	0	0	0
	%	0.0%	0.0%	0.0%
Unavailable Missed Visit / Lost to Follow-up	n	0	0	0
	%	0.0%	0.0%	0.0%
% Accountability= [available/(available + unavailable)]		100.0%	100.0%	100.0%

b. Stability of Outcome

Table 4 shows, 99.1% of myopic astigmatic eyes between 1 and 3 months and 100.0% of myopic astigmatic eyes between 3 and 6 months experienced a change in MRSE of 1.00D or less. Refractive stability was demonstrated by 3 months and confirmed between 3 and 6 months based on the FDA guidance document criterion of >95% having a change in MRSE of ≤ 1.00D between two postoperative intervals.

Table 4. Stability of Manifest Refraction Spherical Equivalent: Entire Cohort of Myopic Astigmatic Eyes

Change in MRSE ≤ 1.00 D Between	1 AND 3 MONTHS (N=232)	3 AND 6 MONTHS (N=232)
n/N	230/232	232/232
%	99.1%	100.0%
Mean Change ± SD	-0.02 ± 0.32	-0.01 ± 0.28
(95% CI)	(-0.06, 0.02)	(-0.05, 0.02)

MRSE = Manifest Refraction Spherical Equivalent CI = 95% Confidence Interval

c. Effectiveness Outcomes

The effectiveness outcomes for UCVA and MRSE by visit are shown in Table 5 for myopic astigmatic eyes. The effectiveness parameters are stratified by preoperative MRSE at 3 and 6 months for myopic astigmatic eyes in Tables 6 and 7, respectively. Overcorrection greater than 1D of MRSE was seen in 7% of the cohort, with 0.4% overcorrected by greater than 2D MRSE at 3 months. Cycloplegic refraction SE overcorrection of greater than 1D was seen in 18% of the eyes, with 2% being overcorrected by greater than 2D at 3 months.

Table 5. Summary of Key Efficacy Variables Over Time For Myopic Astigmatic Eyes

Efficacy Variables		1 Month	3 Months	6 Months
UCVA 20/20 or better for eyes with preop BSCVA of 20/20 or better	n/N % CI	176/225 78.2% (72.3, 83.4)	182/225 80.9% (75.1, 85.8)	193/225 85.8% (80.5, 90.1)
UCVA 20/20 or better	n/N % CI	177/232 76.3% (70.3, 81.6)	184/232 79.3% (73.5, 84.3)	195/232 84.1% (78.7, 88.5)
UCVA 20/25 or better	n/N % CI	217/232 93.5% (89.6, 96.3)	223/232 96.1% (92.8, 98.2)	219/232 94.4% (90.6, 97.0)
UCVA 20/40 or better	n/N % CI	229/232 98.7% (96.3, 99.7)	230/232 99.1% (96.9, 99.9)	226/232 97.4% (94.5, 99.0)
MRSE ±0.50D of intended	n/N % CI	186/232 80.2% (74.5, 85.1)	181/232 78.0% (72.1, 83.2)	186/232 80.2% (74.5, 85.1)
MRSE ±1.00D of intended	n/N % CI	213/232 91.8% (87.5, 95.0)	214/232 92.2% (88.0, 95.3)	213/232 91.8% (87.5, 95.0)
MRSE ±2.00D of intended	n/N % CI	231/232 99.6% (97.6, 100.0)	231/232 99.6% (97.6, 100.0)	231/232 99.6% (97.6, 100.0)

UCVA = Uncorrected Visual Acuity BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent CI = 95% Confidence Interval D = Diopter

Table 6. Summary of Key Efficacy Variables at 3 Months For Myopic Astigmatic Eyes Stratified by Diopter of Preoperative Manifest Refraction Spherical Equivalent

Efficacy Variables		0 to -0.99D	-1 to -1.99D	-2 to -2.99D	-3 to -3.99D	-4 to -4.99D	-5 to -5.99D	-6 to -6.99D	-7 to -7.99D	-8 to -8.99D	-9 to -9.99D	-10 to -10.63D	Total
UCVA ≥ 20/20 if preop BSCVA ≥ 20/20	n/N	2/2	27/31	39/46	29/36	32/38	23/32	10/13	14/18	3/4	2/2	1/3	182/225
	%	100.0%	87.1%	84.8%	80.6%	84.2%	71.9%	76.9%	77.8%	75.0%	100.0%	33.3%	80.9%
UCVA 20/20 or better	n/N	2/2	27/32	39/47	30/38	32/39	24/33	10/13	14/19	3/4	2/2	1/3	184/232
	%	100.0%	84.4%	83.0%	78.9%	82.1%	72.7%	76.9%	73.7%	75.0%	100.0%	33.3%	79.3%
UCVA 20/25 or better	n/N	2/2	32/32	44/47	38/38	37/39	31/33	12/13	18/19	4/4	2/2	3/3	223/232
	%	100.0%	100.0%	93.6%	100.0%	94.9%	93.9%	92.3%	94.7%	100.0%	100.0%	100.0%	96.1%
UCVA 20/40 or better	n/N	2/2	32/32	46/47	38/38	39/39	33/33	12/13	19/19	4/4	2/2	3/3	230/232
	%	100.0%	100.0%	97.9%	100.0%	100.0%	100.0%	92.3%	100.0%	100.0%	100.0%	100.0%	99.1%
MRSE ±0.50D of intended	n/N	2/2	32/32	39/47	28/38	34/39	21/33	9/13	12/19	1/4	1/2	2/3	181/232
	%	100.0%	100.0%	83.0%	73.7%	87.2%	63.6%	69.2%	63.2%	25.0%	50.0%	66.7%	78.0%
MRSE ±1.00D of intended	n/N	2/2	32/32	45/47	36/38	36/39	30/33	11/13	15/19	3/4	2/2	2/3	214/232
	%	100.0%	100.0%	95.7%	94.7%	92.3%	90.9%	84.6%	78.9%	75.0%	100.0%	66.7%	92.2%
MRSE ±2.00D of intended	n/N	2/2	32/32	47/47	38/38	39/39	33/33	13/13	18/19	4/4	2/2	3/3	231/232
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	94.7%	100.0%	100.0%	100.0%	99.6%

UCVA = Uncorrected Visual Acuity BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent D = Diopter

Table 7. Summary of Key Efficacy Variables at 6 Months For Myopic Astigmatic Eyes Stratified by Diopter of Preoperative Manifest Refraction Spherical Equivalent

Efficacy Variables		0 to -0.99D	-1 to -1.99D	-2 to -2.99D	-3 to -3.99D	-4 to -4.99D	-5 to -5.99D	-6 to -6.99D	-7 to -7.99D	-8 to -8.99D	-9 to -9.99D	-10 to -10.63D	Total
UCVA ≥ 20/20 if preop BSCVA ≥ 20/20	n/N	2/2	30/31	40/46	33/36	32/38	23/32	11/13	15/18	3/4	2/2	2/3	193/225
	%	100.0%	96.8%	87.0%	91.7%	84.2%	71.9%	84.6%	83.3%	75.0%	100.0%	66.7%	85.8%
UCVA 20/20 or better	n/N	2/2	30/32	40/47	33/38	32/39	24/33	11/13	16/19	3/4	2/2	2/3	195/232
	%	100.0%	93.8%	85.1%	86.8%	82.1%	72.7%	84.6%	84.2%	75.0%	100.0%	66.7%	84.1%
UCVA 20/25 or better	n/N	2/2	32/32	42/47	37/38	35/39	32/33	12/13	18/19	4/4	2/2	3/3	219/232
	%	100.0%	100.0%	89.4%	97.4%	89.7%	97.0%	92.3%	94.7%	100.0%	100.0%	100.0%	94.4%
UCVA 20/40 or better	n/N	2/2	32/32	45/47	38/38	36/39	33/33	12/13	19/19	4/4	2/2	3/3	226/232
	%	100.0%	100.0%	95.7%	100.0%	92.3%	100.0%	92.3%	100.0%	100.0%	100.0%	100.0%	97.4%
MRSE ±0.50D of intended	n/N	2/2	30/32	38/47	30/38	33/39	25/33	10/13	13/19	2/4	1/2	2/3	186/232
	%	100.0%	93.8%	80.9%	78.9%	84.6%	75.8%	76.9%	68.4%	50.0%	50.0%	66.7%	80.2%
MRSE ±1.00D of intended	n/N	2/2	32/32	45/47	34/38	35/39	31/33	11/13	15/19	3/4	2/2	3/3	213/232
	%	100.0%	100.0%	95.7%	89.5%	89.7%	93.9%	84.6%	78.9%	75.0%	100.0%	100.0%	91.8%
MRSE ±2.00D of intended	n/N	2/2	32/32	47/47	38/38	39/39	33/33	13/13	18/19	4/4	2/2	3/3	231/232
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	94.7%	100.0%	100.0%	100.0%	99.6%

UCVA = Uncorrected Visual Acuity
BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent
D = Diopter

A comparison of **postoperative** uncorrected visual acuity (UCVA) to **preoperative** best spectacle corrected visual acuity (BSCVA) after CustomCornea® LASIK surgery is presented in Table 8. A postoperative UCVA equal to or better than the preoperative BSCVA was achieved in 60.3% of eyes at 3 months and 67.2% at 6 months.

Table 8. Postoperative Uncorrected Visual Acuity Compared to Preoperative Best Spectacle Corrected Visual Acuity for Myopic Astigmatic Eyes

		3 MONTHS	6 MONTHS
UCVA **2 Lines Better** Than Preop BSCVA	n/N %	2/232 0.9%	3/232 1.3%
UCVA **1 Line Better** Than Preop BSCVA	n/N %	37/232 15.9%	50/232 21.6%
UCVA **Equal to** Preop BSCVA	n/N %	101/232 43.5%	103/232 44.4%
UCVA **1 Line Worse** Than Preop BSCVA	n/N %	61/232 26.3%	55/232 23.7%
UCVA **2 Lines Worse** Than Preop BSCVA	n/N %	26/232 11.2%	10/232 4.3%
UCVA **>2 Lines Worse** Than Preop BSCVA	n/N %	5/232 2.2%	11/232 4.7%

Efficacy of astigmatic correction was evaluated at the 3-month point of stability and additionally at 6 months for myopic astigmatic eyes. The mean percentage reduction in absolute cylinder was 65.7% at 3 months and 66.8% at 6 months for all astigmatic eyes (Table 9). A greater percentage reduction was observed in eyes with higher preoperative cylinder. The correction ratio was 1.04 for all astigmatic eyes at 3 months and 1.03 at 6 months, approaching the ideal value of 1.0 (Table 10).

Table 9. Mean Percentage Reduction of Absolute (Non-Vector) Cylinder for Myopic Astigmatic Eyes

Preoperative Cylinder	N	3 MONTHS	6 MONTHS
		Mean %	Mean %
All	232	65.7%	66.8%
0 to 0.50D	45	53.3%	60.0%
>0.50 to 1.00D	71	58.0%	58.5%
>1.00 to 2.00D	84	71.6%	70.9%
>2.00 to 3.00D	22	84.1%	83.6%
>3.00 to 4.00D	8	85.9%	86.9%
>4.00 to 5.00D	2	81.9%	85.0%

Table 10. Vector Analysis for Myopic Astigmatic Eyes			
Preoperative Cylinder	N	3 MONTHS	6 MONTHS
		Mean ± SD Correction Ratio	Mean ± SD Correction Ratio
All	232	1.04 ± 0.37	1.03 ± 0.37
0 to 0.50D	45	1.08 ± 0.60	1.11 ± 0.56
>0.50 to 1.00D	71	1.04 ± 0.38	0.99 ± 0.43
>1.00 to 2.00D	84	1.01 ± 0.23	1.01 ± 0.23
>2.00 to 3.00D	22	1.04 ± 0.14	1.03 ± 0.13
>3.00 to 4.00D	8	1.04 ± 0.14	1.05 ± 0.13
>4.00 to 5.00D	2	1.12 ± 0.01	1.03 ± 0.05

d. Wavefront Outcomes

Table 11 displays the change from preoperative in total wavefront error and in higher-order aberrations through 6th-order for myopic astigmatic eyes. At 3 months, there was an average reduction in total RMS wavefront error by 84.5% and an average increase in higher-order aberrations by 19.4% from preoperative. Six-month data showed similar trends with an average reduction in total RMS wavefront error by 85.0% and an average increase in higher-order aberrations by 20.6% from preoperative. No statistically significant difference was observed in postoperative coma and spherical aberration compared to preoperative levels.

Table 11. Mean Change in Aberrations Up to 6th-Order from Preoperative for Myopic Astigmatic Eyes				
Aberration	3 MONTHS MEAN VALUE (N=232)		6 MONTHS MEAN VALUE (N=232)	
	µm	%	µm	%
Total RMS	-4.76	-84.5%	-4.79	-85.0%
Higher-Order	0.071	19.4%	0.076	20.6%
Coma	0.021	10.1%	0.018	9.1%
Trefoil	0.028	17.7%	0.029	18.5%
Spherical Aberration	-0.012	-6.8%	0.000	0.1%
Secondary Astigmatism	0.044	64.2%	0.048	70.6%
Tetrafoil	0.047	67.9%	0.047	67.5%
Combined 5th and 6th Order	0.066	103.3%	0.064	100.3%

RMS = Root Mean SquareWavefront analysis diameter = 6.0 mm

All eyes had a reduction in total wavefront RMS error and 42.2% had a postoperative reduction in higher-order aberrations at 3 and 6 months, as shown in Table 12.

Table 12. Percentage of Eyes with Reduced Aberrations Up to 6th-Order From Preoperative for Myopic Astigmatic Eyes

Aberration	3 MONTHS N = 232	6 MONTHS N = 232
Total RMS	100.0%	100.0%
Higher-Order	42.2%	42.2%
Coma	47.4%	50.0%
Trefoil	47.0%	44.8%
Spherical Aberration	53.9%	51.7%
Secondary Astigmatism	30.2%	31.0%
Tetrafoil	28.9%	30.2%
Combined 5th and 6th Order	7.8%	8.2%

RMS = Root Mean SquareWavefront analysis diameter = 6.0 mm

The CustomCornea® LASIK eyes were compared to Conventional LASIK eyes treated in the study over the same preoperative refractive range of up to -7.00D sphere with -0.50D to -2.50D cylinder. Wavefront aberrations were analyzed up to 4th-order for comparison.

The amount of postoperative higher-order aberrations was significantly less for the CustomCornea® LASIK eyes than for the Conventional LASIK eyes. The average increase in higher-order aberrations after surgery was 6.9% at 3 months and 8.1% at 6 months following CustomCornea® LASIK compared to 55.4% at 3 months and 56.9% at 6 months following Conventional LASIK (Table 13).

Table 13. Mean Change in Aberrations Up to 4th-Order from Preoperative for Myopic Astigmatic Eyes

Aberration	3 MONTHS MEAN VALUE				6 MONTHS MEAN VALUE			
	CustomCornea® N = 197		Conventional N = 84		CustomCornea® N = 197		Conventional N = 88	
	µm	%	µm	%	µm	%	µm	%
Total RMS	-4.46	-84.7	-3.31	-75.1	-4.49	-85.3	-3.30	-74.8
Higher-Order	0.025	6.9	0.184	55.4	0.029	8.1	0.189	56.9
Coma	0.003	1.5	0.098	51.6	-0.003	-1.5	0.076	40.0
Trefoil	0.007	4.4	0.004	2.3	0.011	6.9	0.016	9.3
Spherical Aberration	-0.015	-8.6	0.180	139.5	-0.004	-2.3	0.199	154.3
Secondary Astigmatism	0.036	52.9	0.024	38.1	0.038	55.9	0.030	47.6
Tetrafoil	0.035	49.3	0.042	57.5	0.036	50.7	0.030	41.1

RMS = Root Mean SquareWavefront analysis diameter = 6.0 mm

A vision simulation program was used to model the effect of various wavefront errors on a simulated eye chart image for CustomCornea® and Conventional LASIK myopic astigmatic eyes. Visual comparisons of letter charts blurred by higher-order aberrations suggest that the benefit of smaller amounts of higher-order aberrations after wavefront-guided CustomCornea® LASIK surgery compared to Conventional LASIK corresponds to approximately 0.2D of defocus on average.

For approximately one-half of patients, CustomCornea® LASIK reduced higher-order aberrations from baseline levels prior to surgery. The percentage of patients with reduced higher-order aberrations after surgery compared to before surgery was 47.7% at 3 months and 49.2% at 6 months for CustomCornea® LASIK compared to 17.9% at 3 months and 19.3% at 6 months for Conventional LASIK (Table 14).

Table 14. Percentage of Eyes with Reduced Aberrations Up to 4th-Order From Preoperative for Myopic Astigmatic Eyes

Aberration	3 MONTHS		6 MONTHS	
	CustomCornea® N = 197	Conventional N = 84	CustomCornea® N = 197	Conventional N = 88
Total RMS	100.0%	96.4%	100.0%	97.7%
Higher-Order	47.7%	17.9%	49.2%	19.3%
Coma	50.8%	34.5%	53.8%	38.6%
Trefoil	49.2%	52.4%	47.2%	47.7%
Spherical Aberration	55.3%	16.7%	54.3%	13.6%
Secondary Astigmatism	32.0%	40.5%	33.0%	25.0%
Tetrafoil	31.0%	25.0%	32.0%	37.5%

RMS = Root Mean Square Wavefront analysis diameter = 6.0 mm

e. Safety Outcomes

The key safety outcomes for all 331 eyes in the safety cohort are presented in Table 15. These same parameters for all eyes are stratified by preoperative MRSE at 3 and 6 months in Tables 16 and 17, respectively.

The safety data meet the safety criteria established in the FDA guidance document of less than 5% of eyes with a loss of >2 lines of BSCVA, less than 1% having a BSCVA of worse than 20/40, and less than 5% having induced astigmatism >2D.

Table 15. Summary of Key Safety Variables Over Time For All Eyes

Safety Variables		1 Month	3 Months	6 Months
Loss of >2 Lines BSCVA	n/N % CI	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)
Loss of 2 Lines BSCVA	n/N % CI	8/331 2.4% (1.0, 4.7)	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)
BSCVA worse than 20/40	n/N % CI	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)
Increase >2D cylinder magnitude	n/N % CI	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)	0/331 0.0% (0.0, 1.1)
BSCVA worse than 20/25 if 20/20 or better preoperatively	n/N % CI	0/323 0.0% (0.0, 1.1)	0/323 0.0% (0.0, 1.1)	0/323 0.0% (0.0, 1.1

BSCVA = Best Spectacle Corrected Visual AcuityCI = 95% Confidence IntervalD = Diopter

Table 16. Summary of Key Safety Variables at 3 Months For All Eyes Stratified by Diopter of Preoperative Manifest Refraction Spherical Equivalent

Safety Variables		0 to -0.99D	-1 to -1.99D	-2 to -2.99D	-3 to -3.99D	-4 to -4.99D	-5 to -5.99D	-6 to -6.99D	-7 to -7.99D	-8 to -8.99D	-9 to -9.99D	-10 to -10.63D	Total
Loss of >2 Lines BSCVA	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/40	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase >2D cylinder magnitude	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA<20/25 if ≥20/20 preop	n/N	0/2	0/55	0/55	0/57	0/51	0/44	0/21	0/24	0/7	0/4	0/3	0/323
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

BSCVA = Best Spectacle Corrected Visual AcuityD = Diopter

Table 17. Summary of Key Safety Variables at 6 Months For All Eyes Stratified by Diopter of Preoperative Manifest Refraction Spherical Equivalent

Safety Variables		0 to -0.99D	-1 to -1.99D	-2 to -2.99D	-3 to -3.99D	-4 to -4.99D	-5 to -5.99D	-6 to -6.99D	-7 to -7.99D	-8 to -8.99D	-9 to -9.99D	-10 to -10.63D	Total
Loss of >2 Lines BSCVA	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/40	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase >2D cylinder magnitude	n/N	0/2	0/56	0/56	0/60	0/52	0/45	0/21	0/25	0/7	0/4	0/3	0/331
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA<20/25 if ≥20/20 preop	n/N	0/2	0/55	0/55	0/57	0/51	0/44	0/21	0/24	0/7	0/4	0/3	0/323
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

BSCVA = Best Spectacle Corrected Visual AcuityD = Diopter

Best spectacle corrected visual acuity (BSCVA) was measured using a standard (high-contrast) visual acuity chart under dim room illumination (10-12 cd/m^2). All eyes had a BSCVA of 20/25 or better at 3 months and 20/32 or better at 6 months. At 3 and 6 months, respectively, 92.7% and 91.5% of eyes had no change or a gain in BSCVA from preoperative (Table 18).

Table 18. Change in Best Spectacle Corrected Visual Acuity for All Eyes

		1 MONTH	3 MONTHS	6 MONTHS
Decrease >2 Lines	n/N %	0/331 0.0%	0/331 0.0%	0/331 0.0%
Decrease 2 Lines	n/N %	8/331 2.4%	0/331 0.0%	0/331 0.0%
Decrease 1 Line	n/N %	35/331 10.6%	24/331 7.3%	28/331 8.5%
No change	n/N %	179/331 54.1%	185/331 55.9%	158/331 47.7%
Increase 1 Line	n/N %	107/331 32.3%	116/331 35.0%	137/331 41.4%
Increase 2 Lines	n/N %	2/331 0.6%	6/331 1.8%	8/331 2.4%
Increase >2 Lines	n/N %	0/331 0.0%	0/331 0.0%	0/331 0.0%

Low contrast BSCVA was measured using a 10% low contrast visual acuity chart under dim room illumination. A trend for improvement in low contrast BSCVA was also observed following treatment with more eyes demonstrating a gain of ≥1 line as compared to a loss of ≥1 line at 3 and 6 months (Table 19).

Table 19. Change in Low Contrast Best Spectacle Corrected Visual Acuity for All Eyes

		3 MONTHS	6 MONTHS
Decrease >2 Lines	n/N %	3/331 0.9%	2/331 0.6%
Decrease 2 Lines	n/N %	14/331 4.2%	10/331 3.0%
Decrease 1 Line	n/N %	49/331 14.8%	29/331 8.8%
No change	n/N %	123/331 37.2%	128/331 38.7%
Increase 1 Line	n/N %	121/331 36.6%	126/331 38.1%
Increase 2 Lines	n/N %	20/331 6.0%	29/331 8.8%
Increase >2 Lines	n/N %	1/331 0.3%	7/331 2.1%

A summary of adverse events and complications is shown in Table 20. The data meet the safety criteria established in the FDA guidance document of less than 1% occurrence of each type of adverse event and <5% overall.

Table 20. Summary of Adverse Events and Complications At Any Postoperative Visit for All Eyes

ADVERSE EVENTS	n/N	%
Corneal cap edema at one month or later (related to microkeratome)	2/331	0.6%
Free Cap (related to microkeratome)	1/331	0.3%
Miscreated flap (related to microkeratome)	1/332 §	0.3%
COMPLICATIONS		
Corneal edema at one week to less than one month	5/331	1.5%
Diffuse lamellar keratitis	3/331	0.9%
Double/ghost images	2/331	0.6%
Epithelium in the interface	3/331	0.9%
Foreign body sensation at one month or later	2/331	0.6%
Striae	1/331	0.3%

§ One eye did not receive laser ablation after the miscreated flap and was not included in the primary cohort analysis.

There were no reports of the following adverse events and complications in the clinical study:

- pain at one month or later;
- corneal epithelial defect at one month or later;
- corneal infiltrate or ulcer;
- late onset of corneal haze at six months with a loss of 2 or more lines of best spectacle corrected visual acuity (BSCVA);
- loss of more than 10 letters (more than 2 lines) of BSCVA at six months;
- epithelium in the interface with a loss of 2 or more lines of BSCVA;
- melting of the flap;
- misaligned flap;
- intraocular pressure (IOP) of more than 25 mmHg;
- IOP increase of more than 10 mmHg above baseline;
- retinal detachment;
- retinal vascular accident.

f. Additional Safety Outcomes

All eyes had an IOP of ≤ 21 mmHg preoperatively and at all postoperative visits. There was no postoperative increase in IOP from preoperative of > 7 mmHg at 1 month and > 5 mmHg at 3 or 6 months. No corneal haze greater than trace was observed at any postoperative interval and there was no BSCVA loss of ≥ 2 lines associated with haze.

Corneal and anterior segment findings that were reported at 1 month or later included superficial punctate keratitis (SPK) ≥ Grade 1 (3.0%), allergic conjunctivitis (0.6%), and viral conjunctivitis (0.6%). There were no clinically significant crystalline lens, vitreous or fundus findings noted postoperatively that were not present preoperatively.

g. Contrast Sensitivity

Contrast sensitivity was measured under both photopic and mesopic conditions using CSV-1000 (VectorVision[7]) (Table 21). A clinically significant change from preoperative was defined as > 2 levels (> 0.3 log) at two or more spatial frequencies.

Under photopic conditions, the percentage of eyes with a gain or loss in contrast sensitivity was approximately equal at 3 months, but more eyes had a gain compared to loss at 6 months. Photopic contrast sensitivity gain was observed in 6.0% of eyes at 3 months and 6.5% at 6 months, whereas loss was observed in 6.5% and 1.7% of eyes at these respective visits. Under mesopic conditions, a higher percentage of eyes had a postoperative gain as compared to loss. Mesopic contrast sensitivity gain was observed in 18.5% of eyes at 3 months and 22.4% at 6 months, whereas loss was observed in 8.6% and 7.3% of eyes at these respective visits. At 6 months, 98.3% of eyes had no change or improvement under photopic conditions and 92.7% had no change or improvement under mesopic conditions.

Table 21. Change of >2 Levels (> 0.3 Log) on CSV-1000 at 2 or More Spatial Frequencies for Myopic Astigmatic Eyes

	Photopic Conditions			
	Decrease		**Increase**	
	3 MONTHS	**6 MONTHS**	**3 MONTHS**	**6 MONTHS**
n/N	15/232	4/232	14/232	15/232
%	6.5%	1.7%	6.0%	6.5%
	Mesopic Conditions*			
	Decrease		**Increase**	
	3 MONTHS	**6 MONTHS**	**3 MONTHS**	**6 MONTHS**
n/N	20/232	17/232	43/232	52/232
%	8.6%	7.3%	18.5%	22.4%

*Mesopic illumination with neutral density filters in front of eyes

[7] *VectorVision* TM of VectorVision

h. Patient Self-Evaluation

Patients were also asked to rate symptoms without glasses or contact lenses after surgery as compared to with glasses or contact lenses before surgery, as shown in Table 22.

Table 22. Postoperative Change in Subjective Symptoms without Correction vs. Preoperative with Correction for Myopic Astigmatic Eyes

3 MONTHS (N=232)					
Symptom	**Significantly Better**	**Better**	**No Change**	**Worse**	**Significantly Worse**
Blurring of Vision	9.1%	10.3%	67.2%	12.1%	1.3%
Burning*	6.1%	11.7%	77.0%	5.2%	0.0%
Double Vision†	7.4%	3.0%	81.8%	5.2%	2.6%
Dryness	7.8%	14.7%	52.2%	23.3%	2.2%
Excessive Tearing*	5.2%	6.1%	88.7%	0.0%	0.0%
Fluctuation of Vision	9.1%	10.8%	55.6%	22.4%	2.2%
Glare†	6.1%	14.3%	57.1%	20.8%	1.7%
Gritty Feeling	7.8%	9.9%	72.0%	9.5%	0.9%
Halos	6.5%	14.2%	58.2%	19.8%	1.3%
Headache	6.0%	9.9%	78.9%	5.2%	0.0%
Light Sensitivity	4.3%	14.7%	58.6%	21.6%	0.9%
Night Driving Difficulty	7.3%	21.6%	59.9%	9.5%	1.7%
Pain	6.0%	8.6%	81.9%	3.4%	0.0%
Redness	6.5%	10.3%	77.2%	5.6%	0.4%
6 MONTHS (N=232)					
Blurring of Vision	10.8%	10.3%	62.5%	15.9%	0.4%
Burning†	7.4%	11.3%	77.1%	3.5%	0.9%
Double Vision	9.5%	4.3%	78.9%	6.9%	0.4%
Dryness	11.2%	14.2%	55.2%	17.7%	1.7%
Excessive Tearing*	6.5%	4.3%	89.1%	0.0%	0.0%
Fluctuation of Vision	11.6%	9.9%	60.3%	16.4%	1.7%
Glare	9.9%	18.5%	58.2%	13.4%	0.0%
Gritty Feeling	12.1%	10.3%	73.3%	4.3%	0.0%
Halos	10.8%	17.7%	54.3%	16.4%	0.9%
Headache	9.9%	12.1%	74.6%	2.6%	0.9%
Light Sensitivity	7.8%	18.5%	57.3%	15.9%	0.4%
Night Driving Difficulty	15.9%	20.3%	53.4%	10.3%	0.0%
Pain*	8.3%	9.6%	79.6%	2.6%	0.0%
Redness	9.1%	16.8%	72.8%	1.3%	0.0%

*N=230†N=231

Postoperative quality of vision without correction was rated as unchanged, better, or significantly better than preoperative quality of vision with correction in 93.1% of patients at 3 months and 94.4% at 6 months (Table 23). There were 88.3% of the patients at 3 months and 87.9% at 6 months reported they were satisfied or extremely satisfied with their results (Table 24). Distance correction was never worn by 93.9% of the patients at 3 months and 94.8% at 6 months (Table 25).

Table 23. Postoperative Quality of Vision without Correction vs. Preoperative with Correction for Myopic Astigmatic Eyes

	3 MONTHS (N=231)	6 MONTHS (N=232)
Significantly Better	55.8%	63.8%
Better	28.1%	21.1%
Same	9.1%	9.5%
Worse	5.2%	5.2%
Significantly Worse	1.7%	0.4%

Table 24. Postoperative Satisfaction with Surgery for Myopic Astigmatic Eyes

	3 MONTHS (N=230)	6 MONTHS (N=232)
Extremely Satisfied	57.8%	67.7%
Satisfied	30.4%	20.3%
Neutral/Not Sure	8.7%	6.9%
Unsatisfied	1.3%	5.2%
Extremely Unsatisfied	1.7%	0.0%

Table 25. Postoperative Frequency of Distance Correction for Myopic Astigmatic Eyes

	3 MONTHS (N=231)	6 MONTHS (N=230)
Never	93.9%	94.8%
Seldom	3.5%	0.0%
Frequently	0.9%	3.5%
Constantly	1.7%	1.7%

i. Retreatments

There are insufficient data for retreatment to establish safety and effectiveness.

j. Statistical Analysis Outcomes

Logistic regression analysis was performed to investigate the association between various baseline and demographic characteristics and outcomes related to CustomCornea® LASIK for correction of myopic astigmatism. This approach provided the ability to assess the effect of one variable while controlling for other factors that influence outcome. Outcomes assessed included uncorrected visual acuity (UCVA), accuracy of manifest refraction spherical equivalent (MRSE), and loss of best spectacle corrected visual acuity (BSCVA). Since there was no loss of 2 or more lines of BSCVA at 3 or 6 months, statistical analysis could not be performed on this outcome.

Statistical analysis showed that age, preoperative cylinder, and room temperature were found to be associated with achieving a UCVA of 20/20 or better at 6 months. Age was also associated with a UCVA of 20/40 or better at 6 months. While the FDA guidance document does not specify performance requirements for a UCVA of 20/20 or better, the results for all subgroups, met or exceeded the FDA guidance standard that requires at least 85% of eyes to achieve a UCVA of 20/40 or better.

At 6 months, a UCVA of 20/20 or better and a UCVA of 20/40 or better were more likely to be achieved in subjects less than 50 years of age, although all ages stratified by decade met the FDA guidance standard for UCVA of 20/40 or better. A UCVA of 20/20 or better was more likely to be achieved in eyes with less than -4D preoperative cylinder; however, all cylinder subgroups by diopter exceeded the FDA guidance standard for a UCVA of 20/40 or better. The mean room temperature during surgery for eyes with a UCVA of 20/20 or better was slightly higher than for eyes that did not achieve 20/20, although the mean difference between the two groups was < 1°F.

Statistical analysis showed that age, preoperative sphere, temperature and humidity were significantly associated with an accuracy of MRSE within 0.50D of emmetropia. At 6 months, the results for all subgroups, except for one sphere subgroup with 3 eyes, met or exceeded the FDA guidance standard of ≥ 50% of eyes with an MRSE within 0.50D.

While subjects less than 50 years of age were more likely to have an MRSE within 0.50D, all ages stratified by decade met the FDA guidance standard. Eyes with less than -8D preoperative sphere were more likely to achieve an MRSE within 0.50D, although eyes in all other sphere subgroups including eyes with a sphere between -9.0 and -9.75D were within the FDA guidance standard. The mean room temperature during surgery was slightly lower for eyes that had an MRSE within 0.50D than for eyes that did not, but the difference between the groups was < 1°F. Similarly, while the difference between the groups was < 1%, the room humidity during surgery was slightly higher for eyes that had an MRSE within 0.50D than for eyes that did not.

Age, preoperative sphere, gender and humidity were associated with an accuracy of MRSE within 1.0D of emmetropia. At 6 months, the results for all subgroups, except for one sphere subgroup, met or exceeded the FDA guidance standard of ≥ 75% of eyes with an MRSE within 1.0D.

Subjects less than 50 years of age were more likely to have an MRSE within 1.0D; however, all ages stratified by decade met the FDA guidance standard. Eyes in all sphere subgroups up to -9.75D met the FDA guidance standard, except for the range between -7 to -7.99D preoperative sphere. Slightly more males than females achieved an MRSE within 1.0D; however, the mean preoperative MRSE was higher for females who did not achieve an MRSE within 1.0D. An MRSE within 1.0D was more likely to be achieved at lower room humidity during surgery than for eyes that were not within 1.0D, although the mean difference between the two groups was < 3%.

The same factors, age, preoperative sphere, gender and humidity, were also associated with overcorrection of the MRSE by more than 1.0D at 6 months. Higher room humidity was associated with undercorrection of the MRSE by more than 1.0D; however, only three eyes had undercorrection more than 1.0D at 6 months.

k. Surgical Issues

There were two eyes with reported problems during surgery related to the microkeratome creation of the flap. All treated eyes had complete laser ablation during the same surgery session and were tracked throughout the ablation. During the laser treatment of three eyes, there were system-related messages that had no impact to the surgical treatment or safety risk to the patient.

In addition, there were 36 eyes treated with a single laser system over a period of time when the video was not correctly calibrated, resulting in spherical overcorrection with no associated safety impact. All of these eyes had a BSCVA of 20/20 or better and were within one line of preoperative BSCVA at the last reported visit.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Clinical studies provided reasonable assurance of safety and effectiveness of the LADARVision®4000 Excimer Laser System for wavefront-guided Laser In-Situ Keratomileusis (LASIK) correction of myopic astigmatism when used in accordance with the indications and directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 5 15(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH issued an approval order on June 29, 2004.

XIV. APPROVAL SPECIFICATIONS

- Postapproval Requirements and Restriction: see Approval Order
- Hazard to Health from Use of the Device: see Indications, Contraindications, Warning, Precautions, and Adverse Events in the labeling.
- Direction for use: see labeling.